PATENT
Docket No. 204372000300

CERTIFICATE OF HAND DELIVERY

I hereby certify that this correspondence is being hand filed with the United States Patent and Trademark Office in Washington, D.C. on May 7, 1998.

Thomas G. Wiseman

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the application of:

Lynn E. SPITLER et al.

Serial No.: 08/105,444

Filing Date: 11 August 1993

For: PROSTATIC CANCER VACCINE

Examiner: P. Gambel

Group Art Unit: 1642

SUBMISSION OF ADDITIONAL DATA

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

Applicants are grateful to the Examiner for granting an interview in the above referenced application, as well as in its continuation-in-part, U.S. Serial No. 08/288,057 filed 10 August 1994. During the interview, the possibility of introducing declaratory evidence into the present case which was provided to the Office in the '057 case was discussed. The Examiner kindly agreed to make of record this evidence in the present case.

The present case has been on appeal since 7 August 1995. The last day for filing a reply brief to the Examiner's Answer was 30 June 1996. The declarations included herewith were submitted in the '057 case only in November of 1996. Thus, they could not have been submitted

in the present case during any active phase of the prosecution below, or during any active phase of the appeal when the case was still before the Examiner.

Enclosed herewith are true copies of the declarations submitted in 08/288,057 along with the exhibits thereto. A brief summary of the nature of these declarations and their exhibits is as follows:

Declarations Submitted 4 November 1996

Five declarations were submitted on November 4, 1996. The first, by Dr. Lynn Spitler, reports the results of a small clinical trial using human PSA recombinantly produced in baculovirus. The formulations of this antigen have been trademarked OncoVax P™. Studies on six patients administered OncoVax P™ showed that no adverse reaction was obtained; in the first four patients tested, peripheral blood lymphocytes showed enhanced levels of gamma interferon and interleukin 4 production in response to peptides derived from human PSA. In addition, one patient responded positively to a skin test for delayed-type hypersensitivity against PSA; two patients showed lymphocyte proliferation in response to PSA.

There were four accompanying declarations: those of Drs. Livingston, Bystryn, Mastrangelo and Oldham. All of these declarations verified that while the ideal measurement of an appropriate antitumor response would have been a measurement of cytotoxic lymphocytes, difficulties in obtaining a satisfactory assay were well known and the measurements provided in the Spitler declaration constituted satisfactory substitutes. All four declarants stated that the results claimed in the clinical study provide evidence that the vaccines are likely to be effective in exerting a beneficial effect on patients with prostate tumors or at risk for prostate tumors. They further stated that the efficacy shown for vaccines based on PSA provides evidence that analogous vaccines based on other host tissue antigens such as PSMA and PAP would behave in a similar way.

Declarations Submitted 27 August 1997

An additional declaration by Dr. Lynn Spitler reported the results of four small clinical studies using OncoVax P™ . The first trial is the same as that reported in the declaration filed November 4, 1996 and the present declaration adds the detail that one patient showed skin test sensitivity to PSA with a diameter of erythema of 18mm and a diameter of induration of 10mm. The OncoVax P™ formulation in this trial was a liposomal formulation containing lipid A and was administered intramuscularly.

The second trial used the same formulation with an intravenous route and one in five patients showed sensitivity in a skin test to PSA (a measure of cellular immune response). The third trial utilized a formulation with GM-CSF as adjuvant and intramuscular administration was used. All four evaluable patients in the study showed skin reactivity with a mean diameter of erythema of 37mm. In the fourth trial, the patients were also treated with cyclophosphamide, the formulation contained BCG and was administered intracutaneously. Four of the five patients in the study showed skin tests with a mean diameter of erythema of 17mm.

Also submitted on August 27, 1997 was the declaration of Dr. Gary Matyas who reported the result, of OncoVax P™ administration in a murine model system. Spleen cells from mice immunized with recombinant human PSA and lipid A as adjuvant were harvested. The spleen cells were able to exert a cytotoxic effect on murine target cells transfected with constructs which effect the expression of human PSA peptides at their surface. Thus, human PSA was able to effect a cytotoxic T-cell response in these mice. It was necessary to use murine cells as targets as the recognition by CTL of target cells is HLA restricted.

Declaration Submitted 29 April 1998

At the above-mentioned interview, applicants entered into the record an additional declaration of Dr. Lynn Spitler reporting the results of an additional, fifth clinical study using OncoVax P^{TM}, wherein the liposomal preparation was emulsified with mineral oil. The results of this trial showed a dramatic cellular response in all five patients in the study. The T-cell response was monitored both by a skin sensitivity test and by the ability of lympocytes isolated from the patients to proliferate in response to PSA. Dr. Spitler's declaration also contains an exhibit of four more or less randomly chosen articles which demonstrate that T-cell response as measured by skin sensitivity to a tumor associated antigen is correlated with increased survival and/or tumor suppression.

Summary of Declaration Evidence

Taken as a whole, the declarations submitted report the results of five clinical mini-trials and in a murine model, using OncoVax P^{TM} , which contains recombinant human PSA as the active ingredient, formulated in various ways and administered in various ways. T-cell responses were obtained in patients in all studies; the fifth clinical study showed dramatic and consistent T-cell responses. The declaration evidence also demonstrates that T-cell response is correlated with an antitumor effect.

Conclusion

Applicants again wish to express their appreciation to the Examiner for his permission to enter this declaratory evidence into the record. As stated above, these data were not available during the active prosecution for the Examiner or during the active period of Appeal Brief/Examiner Answer, etc. No claim in this case has been rejected over the art. The only issues before the board relate to enablement and scope. Thus, this declaration evidence is highly pertinent.

Literature Subsequent to the Active Stage of Appeal

Two articles are of interest in addressing the issue of enablement and scope:

Wei, Chungwen, et al., *Cancer Immunol. Immunother.* (1996), 42:362-368. This work shows that immunization of mice with a PSA expressing tumor cell line resulted in a memory response to PSA which protected against subsequent challenge with PSA-expressing, but not wild-type tumors. Further, immunization with PSA expressing tumor cells resulted in a generation of primary and memory cytotoxic T-lymphocytes specific for PSA.

Murphy, G., et al., *The Prostate* (1996), 29:371-380. This article showed that another prostate antigen PSMA (prostate specific membrane antigen) is an effective active ingredient. In this study, autologous dendritic cells pulsed with HLA-A0201-specific PSMA peptides did not result in toxicity, but elicited a cellular response against PSMA peptides. The authors conclude that the method has a potential in prostate cancer therapy.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 204372000300. However,

the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

Dated: May 4, 1998

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